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THE COAGULATION OF THE BLOOD AND ANAPHYLACTIC SHOCK

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The phenomenon of anaphylaxis has received a vast amount of study in recent years, but in spite of this we are still far from an adequate explanation of its mechanism. The relation of anaphylaxis to infection, immunity reactions, specific and nonspecific treatment of infections, asthma, skin diseases, food idiosyncrasy and blood transfusion has made it a very important problem in medicine. The relation of anaphylaxis to the coagulation of the blood has also attracted some attention since anaphylactic shock is accompanied by a more or less marked change in the coagulability of the blood. These changes in coagulability have led to interesting ideas concerning the theory of anaphylaxis. The antigen-antibody reaction has been supposed by Doerr[1] to influence the process of coagulation, and he, with others, believes that these changes in coagulation are the direct cause of anaphylactic shock. The coagulation process may cause blood or serum to become toxic for the homologous animal. Schultz[2] has noted that fresh uncoagulated arterial blood has no influence on smooth muscle of the same animal, but as soon as there is evidence of clotting the muscle contracts. These phenomena are interesting and worthy of attention and probably have an important relationship to anaphylaxis. Biedl and Kraus[3] believe the decreased coagulability in anaphylactic shock to be due to a decrease in thromboplastin or to an excess of antithrombin. Lee and Vincent[5] "attribute the alteration of coagulation in anaphylaxis to a definite effect on the blood platelets and not to the introduction of antithrombin." Novy and DeKruif[6] assume that "fibrinogen is transformed into an incoagulable tautomeric

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[1] Wien. klin. Wchnschr., 1912, 25, p. 339.
[2] Bull. 80, Hyg. Lab., U. S. Pub. Health and Mar. Hosp. Serv., 1912.
[3] Wien. klin. Wchnschr., 1909, 22, p. 363.
[4] Jour. Infect. Dis., 1914, 14, p. 476.
[5] Jour. Med. Research, 1915, 27, p. 445.
[6] Jour.. Am. Med. Assn., 1917, 68, p. 1527.

modification." Shattuck[7] found a delayed "prothrombin time," but inconclusive results with antithrombin. His antithrombin tests were made by the method of Hess.[8]

METHODS

The methods used in examining the blood in these experiments were first described by Howell[9] and further discussed by Drinker and Hurwitz[10] and by Minot, Denny and Davis.[11]

The so-called "prothrombin time" is the time required for oxalated plasma to clot after the addition of an optimum amount of calcium. Variations in prothrombin time should not be interpreted, as is often done, to mean changes in the amount of prothrombin only. Variations in antithrombin may influence this time; variations in the amount of thromboplastin may cause marked changes in the prothrombin time. The addition of thromboplastin will decrease the time greatly, while absence of thromboplastin will prevent coagulation entirely. This influence of variations in thromboplastin on the prothrombin time may be very important.

The antithrombin determinations consisted in determining the inhibitory influence exerted by oxalated plasma heated to 60 C. on the action of thrombin on fibrinogen. One drop of heated oxalated plasma was added to 2, 3, 4, and 5 drops of thrombin solution and the mixtures allowed to stand 15 minutes. At the end of this time 7 drops of fibrinogen solution were added to each tube and the clotting time determined. The amount of antithrombin in each specimen was indicated by the average clotting time of the 4 tubes. Comparisons between the antithrombin titer in different experiments cannot be made because different solutions of thrombin and of fibrinogen were used in each experiment. Here again thromboplastin may produce variations, a large amount decreasing the inhibitory influence of antithrombin, a small amount having the reverse effect.

The thrombin used in these determinations was prepared by the method of Howell,[12] and some difficulty, traced finally to poor fibrinogen, was encountered in obtaining a satisfactory thrombin-fibrinogen combination. Solutions of purified fibrinogen were found to be more satisfactory than dried plasma and gave a better end point. Fibrinogen from cat's blood proved better than that from dog's and was prepared from carotid blood collected in vaselined centrifuge tubes containing sodium oxalate solution. The plasma was procured by centrifugalization and pure fibrinogen obtained by Howell's[13] modification of Hammarsten's method. A fresh solution was prepared about every 5 days.

Anesthesia was produced by 1.5 gm. of urethan per kg. of body weight. This was found to be very satisfactory, respiratory paralysis never being encountered. In a few experiments 1.7 c c of paraldehyd per kg. was used.

Egg white dissolved in an equal volume of salt solution was employed to produce anaphylaxis.

After the animal was anesthetized, a vein for injection was exposed—the external jugular or the femoral. An artery—the carotid or in a few cases the

[7] Arch. Int. Med., 1917, 20, p. 167.
[8] Jour. Exper. Med., 1915, 21, p. 338.
[9] Arch. Int. Med., 1914, 13, p. 76.
[10] Ibid., 1915, 15, p. 733.
[11] Ibid., 1916, 17, p. 101.
[12] Am. Jour. Physiol., 1913, 32, p. 264.
[13] Ibid., 1910, 26, p. 461.

femoral—to supply the specimens was next exposed, the distal portion ligated and the proximal portion clamped. Care was taken not to crush or injure the vessel. Blood pressure and respiratory tracings were made in a number of the experiments. The specimens of blood were obtained through vaselined glass cannulas. In order to use a fresh, clean cannula for every specimen of blood, each cannula was inserted into the artery and held in place without tying. At each collection of blood two specimens were taken. One—used to determine the coagulation time—was placed at once in a water bath at 37-38 C., and the time noted at which the tube could first be inverted without dislodging the clot. The other was the oxalated specimen. This was drawn directly into a vaselined centrifuge tube containing 1 part of 1% sodium oxalate in physiologic salt solution to 8 parts of blood. After obtaining a normal control specimen the injection was made and the vein clamped off. A second specimen was usually taken as soon after the injection as possible and other specimens followed at varying intervals.

After the death of the animal the oxalated specimens were centrifuged at high speed for 15 minutes and the plasma obtained. Determinations of "prothrombin time" and of antithrombin were made in most cases at once and never later than 3 or 4 hours after collection of the blood. Common glass pipets with rubber bulbs were used in these determinations and when comparable results were wanted the same pipet was used for all specimens, being cleaned and dried before changing from one specimen to another.

The tubes containing the "coagulation time" specimens were set aside and observed from time to time to note the rate of fibrinolysis.

EXPERIMENTS WITH CATS

Cats were sensitized by 3 injections at 2-day intervals of 2 c c of egg white dissolved in an equal volume of physiologic salt solution. Shock was produced by intravenous injection of 5 c c of 50% egg white, 7-10 weeks later. In only one were distinct symptoms of shock with death produced in 10 minutes. Blood pressure tracings in 4 experiments showed the characteristic fall in blood pressure, but instead of remaining down this was recovered from at once. In only the one case mentioned was an incoagulable blood obtained. An average of the other cases showed a slight increase in the coagulation time preceded by a slight decrease. The antithrombin changed very little, the average determinations showing a very slight decrease in amount which might be due to the hemorrhage. The average of the prothrombin times showed a small increase preceded by a slight decrease (Table 1). After shock the plasma showed evidence of hemolysis and there was often a decrease in the "buffy coat."

EXPERIMENTS WITH RABBITS

Rabbits were sensitized by 2 or 3 injections at 2-day intervals of 2 c c of 50% egg white solution. Shock was produced 4-8 weeks later by intravenous injection of 2-6 c c of 50% egg white solution. The results are shown in Table 1. In Exper. 1 there was no increase in coagulation time. In Expers. 8 and 9 the increase was only slight. In the remaining 5 there was a marked increase. In 4 experiments the first specimen taken after shock showed a decreased coagulation time. The average of the antithrombin determinations show a moderate decrease in antithrombin. There was an increase in prothrombin time.

The clotting time of the oxalated specimens was also determined after the addition of optimum amounts of thromboplastin and calcium. By this proce-

TABLE 1

THE EFFECT OF ANAPHYLACTIC SHOCK ON THE COAGULATION TIME AND THE FACTORS OF COAGULATION OF THE BLOOD OF CATS, RABBITS, AND DOGS

	Coagulation Time, Minutes							Time after Shock, Minutes							Antithrombin, Minutes							"Prothrombin Time," Minutes							Clotting Time of Oxalated Plasma Optimum Ca and Thromboplastin, Minutes						
	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
Cat 1	6	3½	7	7½	7			*	2½	5	15	26			65	62	69	66	58			2½	2½	3	3	3										
2	7	3½	9½	7	6	4		*	3	13	25	26	29									3	2½	3	3	3									
3	3	4	4	4				*	3½	15	24				42	42	41	39				3½	3½	3½	3½										
4	3	3	(No clot)					*	1½	8					36	19	46					3	2½	7											
5	7	3	12	10	9			*	2	11	18	45			22	20	22	20	18			4½	3½	6½	5½	6½									
6	6½	4	14	11	10	11		*	1	7	13	42	63		27	25	31	28	24	22		3½	3	6	5½	4½	4								
Rabbit 1	6	6	3	6	6			*	*	3	13	28			68	68	52		44			1½	1½	1½		3½									
3	5½	26	30	29	25	17		*	2	8	13	23	35		117	109	77	82	31			2½	5	5½	5½	4									
4	16	17	15	10	30	26		*	*	*	10	21	37		23	23	23	25	19	14		10	11	11	6	15	14		2½	2½	2½	2½	2½	2½	
5	12	16	51	36	32			*	1	12½	20	26			63	47	44	33	28			7½	9	17	14	13			2	2	2	1¾	2		
6	12	7½	15	60	45	59	30	*	2	3	7½	9	10½	13½	111	99	87	72	66	63	61	10	5	6½	12	20	16	15	1¾	1¾	1¼	1½	1¼	1¼	1
7	8	23	43	53	95			*	1½	5	10	20			48	66	49	58	29			11	13½	17	23	13			1¾	1¾	1½	1¾	1¾		
8	12	6	16	14	13			*	1½	10	20	30			24	25	19	15	15			10	6	15	14	12			2½	2½	2½	2½	2½		
9	8½	19	9½	11	15	14		*	1½	4	13	33	60		43	39	30	31	24	27		35	60	50	19	13	11		1½	1½	1½	1½	1½		
Dog 4	6	6	(Jelly clot in 48 hrs.)					*	1½	2	6	28	63	72	21	25	31	31	30	21	18	2	4½	5½	13½	6½	4½	3	1	1	1¾	1½	1½	1¼	1
5	8		(Jelly clot in 48 hrs.)					*	5	30	60	90	120		32	48	45	48	36	32		2	(no clot)			15	13			1	2½	3	2½	2	2	

TABLE 3

THE EFFECT OF INTRAVENOUS INJECTION OF SEROTOXIN AND PEPTONE ON THE COAGULATION TIME AND FACTORS OF COAGULATION OF THE BLOOD OF RABBITS

	Coagulation Time, Minutes								Time after Shock, Minutes								Antithrombin, Minutes						"Prothrombin Time," Minutes						Clotting Time of Oxalated Plasma Optimum Ca and Thromboplastin, Minutes						
	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	1	2	3	4	5	6	1	2	3	4	5	6	1	2	3	4	5	6	7
Rabbit 13 Serotoxin.	8	11	15	14					*	6	18	25					72	68	72	59			8	12	16½	14										
15 Serotoxin..	3	3½	6½	9½	8				*	3½	8½	9½	20				54	52	50	47	38		4½	4	16	13	12									
14 Peptone...	11	9	6	9	15	15	14	12	*	½	6	16	40	60	90	126	44	43	38	37	33	26	6½	17	11	14	14	14	2	2½	2¼	2½	2	2	
16 Peptone...	5	12	6	10	12				*	1½	10	24	39				30	28	25	20			3½	6	4½	6				2	2½	2	2½			
17 Peptone...	11	16	10½	19					*	1	10	16					39	32	31	34			3	6½	3—	8½				1¼	2	1½	1¼			

* Control specimens taken before shock.

The figures in these tables for antithrombin indicate the average clotting time in minutes of four thrombin-antithrombin-fibrinogen mixtures, using 2, 3, 4 and 5 drops of thrombin.

dure it was intended to show whether the changes in the prothrombin time were due to variations in prothrombin or in thromboplastin. The antithrombin remaining constant one would expect to get variations in the clotting time with variations in prothrombin, or if the prothrombin remained constant to get the same clotting time in all specimens. Any variations in antithrombin would cause a change. Solutions of thromboplastin prepared by the method of Howell[14] were used. These were found to be more satisfactory than purified cephalin prepared by McLean's method.[15] All determinations were made at 37-38 C. To 5 drop portions of the oxalated specimens were added 1, 2, 3, and 4, or 1, 3, and 5 drops of the thromboplastin solution. After standing a few minutes the optimum amount of calcium chlorid solution was added to each tube and the clotting time carefully determined. The results are shown in the last column of Table 1. In all experiments the clotting time was practically the same in all specimens indicating a constant amount of prothrombin.

There was slight hemolysis in the plasma after shock and as a rule a decrease in the "buffy coat."

The following protocol illustrates a typical experiment.

Rabbit 5: Sensitized by intraperitoneal injections of 2 c c of 50% egg white on Oct. 3, 1917, and on Oct. 5, 1917.

Nov. 12, 1917: weight 2.5 kg.

4:18 p. m.: 4 gm. of urethan.

4:46½ p. m.: Control Specimen 1. Coagulation time 12 minutes.

5:01½ p. m.: 2 c c of 50% egg white injected into femoral vein.

5:02½ p. m.: Specimen 2. Coagulation time 16 minutes.

5:14 p. m.: Specimen 3. Coagulation time 51 minutes.

5:22 p. m.: Specimen 4. Coagulation time 36 minutes.

5:28 p. m.: Specimen 5. Coagulation time 32 minutes.

Plasma after shock showed slight hemolysis.

ANTITHROMBIN DETERMINATIONS

Thrombin, Drops	Antithrombin, Drops	Time Interval, Minutes	Fibrinogen, Drops	Coagulation, Minutes
		Specimen 1 (Normal)		
2	1	15	7	95
3	1	15	7	70
4	1	15	7	55
5	1	15	7	34
				Average = 63
		Specimen 2		
2	1	15	7	74
3	1	15	7	54
4	1	15	7	37
5	1	15	7	24
				Average = 47
			Per cent. of normal average = 74	
		Specimen 3		
2	1	15	7	73
3	1	15	7	51
4	1	15	7	32
5	1	15	7	22
				Average = 44
			Per cent. of normal average = 70	

[14] Am. Jour. Physiol., 1912, 31, p. 1.

[15] Ibid., 1916, 41, p. 250.

Specimen 4

2	1	15	7	52
3	1	15	7	37
4	1	15	7	26
5	1	15	7	16

Average = 33

Per cent. of normal average = 52

Specimen 5

2	1	15	7	48
3	1	15	7	31
4	1	15	7	21
5	1	15	7	13

Average = 28

Per cent. of normal average = 44

Control

Thrombin, Drops	Fibrinogen, Drops	Coagulation, Minutes
3	7	3½
5	7	2½

PROTHROMBIN TIME

Specimen 1 (Normal)

Oxalated Plasma Drops	0.5% $CaCl_2$ Drops	Coagulation, Minutes
5	2	15
5	3	7½
5	4	8
5	5	11

Optimum 7½ Minutes

Specimen 2

5	2	9½
5	3	9
5	4	11½
5	5	12

Optimum 9 Minutes

Specimen 3

5	2	25
5	3	17
5	4	24
5	5	22

Optimum 17 Minutes

Specimen 4

5	2	23
5	3	14
5	4	21
5	5	19

Optimum 14 Minutes

Specimen 5

5	2	13
5	3	13½
5	4	14
5	5	25

Optimum 13 Minutes

Clotting time of oxalated plasma on addition of an optimum amount of thromboplastin and calcium:

Oxalated Plasma, Drops	Salt Solution, Drops	Thromboplastin Solution, Drops	0.5% $CaCl_2$ Solution, Drops	Clotting Time, Minutes
		Specimen 1 (Normal)		
5	3	1	3	2
5	2	2	3	2
5	1	3	3	3
5	0	4	3	3¼
			Optimum = 2	minutes
		Specimen 2		
5	3	1	3	2¼
5	2	2	3	2
5	1	3	3	2½
5	0	4	3	3
			Optimum = 2	minutes
		Specimen 3		
5	3	1	3	2
5	2	2	3	2
5	1	3	3	2½
5	0	4	3	3
			Optimum = 2	minutes
		Specimen 4		
5	3	1	3	2
5	2	2	3	1¾
5	1	3	3	2
5	0	4	3	3
			Optimum = 1¾	minutes
		Specimen 5		
5	3	1	3	2¼
5	2	2	3	2½
5	1	3	3	2
5	0	4	3	3
			Optimum = 2	minutes

EXPERIMENTS WITH GUINEA-PIGS

Guinea-pigs were sensitized by one intraperitoneal injection of 1 c c of 1% egg white solution. Shock was produced by an intravenous injection of 1 c c of 50% egg white. It was not practical to collect the specimens through cannulas because the blood flowed too slowly. Therefore, with the animal under urethan anesthesia, the thorax was quickly opened, and while the heart was held with small forceps a cut was made into a ventricle with scissors and a vaselined 5-c c pipet quickly inserted into the heart. The blood was sucked up into the pipet and transferred to the tube for determining the coagulation time and to the tube containing the sodium oxalate solution. For control specimens normal guinea-pigs were used. Such controls would be of questionable value had the changes been less marked. The results are shown in Table 2. In two cases there was no change in the coagulation time. In the others there was an increased coagulation time. Two specimens were incoagulable and one clotted only after 24 hours. Averages showed slightly less antithrombin in the shocked animals than in the normal. The "prothrombin time" was increased.

EXPERIMENTS WITH DOGS

Dog 4 was sensitized by intraperitoneal injections of 5 c c, 5.5 c c, and 5.5 c c of 50% egg white solution on Nov. 12, 14, and 18. On Dec. 27 shock

was produced by an intravenous injection of 20 c c of 50% egg white. The specimen taken one-half minute after shock showed no change in the coagulation time. The other specimens formed a jelly clot after 48 hours. Antithrombin was slightly increased. Prothrombin time was increased. By adding optimum amounts of thromboplastin and calcium to the oxalated plasma a clotting time was obtained which was nearly constant, varying slightly as the antithrombin carried and indicating a constant prothrombin content.

TABLE 2

THE EFFECT OF ANAPHYLACTIC SHOCK ON THE COAGULATION TIME AND THE FACTORS OF COAGULATION OF BLOOD OF GUINEA-PIGS

Normal guinea-pigs were used for controls. The figures for antithrombin indicate the average clotting time in minutes of 4 thrombin-antithrombin-fibrinogen mixtures, using 2, 3, 4, and 5 drops of thrombin.

Guinea-Pigs	Time after Injection, Minutes	Coagulation Time, Minutes	Anti-thrombin, Average	Pro-thrombin, Minutes
12 Normal		3	104	2½
1 Anaphylactic	4	13	74	5
13 Normal		3½	63	3
2 Anaphylactic	1½	9	56	4½
3 Anaphylactic	3	3	74	2½
4 Anaphylactic	6	24 hrs.	51	6
14 Normal		5	67	2
5 Anaphylactic	2	No clot 24 hrs.	50	5
6 Anaphylactic	2	No clot 24 hrs.	46	5½
15 Normal		3½	53	2
7 Anaphylactic	10	3	30	2
8 Anaphylactic	2	12	21	3

Dog 5 was sensitized by intraperitoneal injection of 5 c c, 10 c c, and 10 c c of 50% egg white solution on Nov. 12, 14, and 17. Shock was produced on Dec. 29 by an intravenous injection of 45 c c of 50% egg white. After shock the blood showed a jelly clot in 48 hours. Antithrombin showed a slight increase. The prothrombin time was increased. In specimens 2, 3, and 4 the oxalated plasma failed to clot on addition of calcium chlorid solution. By addition to optimum amounts of thromboplastin and calcium to the oxalated plasma the clotting time varied somewhat as the antithrombin. The results are shown in Table 1.

"SEROTOXIN"

"Serotoxin" was prepared as described by Jobling and Petersen[16] by extracting dog serum with chloroform. In one rabbit (Rabbit 10) death occurred in less than 1 minute after injection of 1 c c. The animal was examined immediately. The heart and some of the large vessels contained solid clots. The coagulation time of the blood before injection was 8 minutes while these clots were found in less than 4 minutes after the injection.

In Rabbits 11 and 12, 0.5 c c of serotoxin was injected. The procedure was the same as in other experiments. The coagulation time, prothrombin time, and antithrombin changed in the same way as in anaphylactic shock. The results are shown in Table 3. After serotoxin injection there was marked hemolysis, greater than ever produced by anaphylactic shock. No buffy coat was present.

[16] Jour. Exper. Med., 1914, 19, p. 480.

KAOLIN SHOCK

A kaolin suspension in salt solution was prepared and allowed to settle a few minutes. The top layer was removed and filtered several times. When 2 c c of this suspension was injected into rabbits intravenously it produced almost immediate death. The animals were examined at once. Almost complete intravascular coagulation had occurred in a very few minutes.

PEPTONE SHOCK

The procedure followed in the foregoing experiments was repeated with 3 rabbits, peptone solution being injected intravenously. The results are shown in Table 3. The coagulation time after initial variations was increased. The prothrombin time was increased. There was no increase in antithrombin, but a slight decrease in all cases. There was no hemolysis in the plasma after peptone injection.

FIBRINOLYSIS

The specimens used for determining coagulation times were preserved and observations made on the rate of fibrinolysis. In normal specimens the average time for solution of the clot was 30-40 days or more. In most cases there was a marked increase in the rate of solution after anaphylactic and peptone shock. In a few cases solution was complete in 4 or 5 days. Jobling, Petersen and Eggstein have shown that during anaphylactic shock[17] and peptone shock[18] there is a mobilization of serum protease and a decrease in antitryptic titer. The antitryptic power of serum has been shown by Jobling and Petersen[19] to be removed by chloroform and ether and to be due to compounds of the unsaturated fatty acids. Antitrypsin obtained by the method of Jobling and Petersen was found to possess no antithrombic activity but did possess some thromboplastic action, probably due to contamination. Minot[20] has shown that chloroform and ether render antithrombin inactive but he was unable to recover any antithrombin from such extracts.

DISCUSSION

The antithrombin changes in these experiments were not great. With dogs the antithrombin was increased somewhat. With other animals there was, as a rule, a slight but definite decrease, although the coagulation time and the prothrombin time were increased. This decrease in antithrombin may have been due to the hemorrhage, Drinker and Drinker[21] having shown that hemorrhage produces a decreased coagulation time accompanied by a decrease in antithrombin. The increased coagulation time after anaphylactic shock is therefore not due to an increase in antithrombin, although it may be possible to have an increase in some animals which would help to retard coagulation.

[17] Jour. Exper. Med., 1915, 22, p. 401.
[18] Ibid., 1915, 22, p. 597.
[19] Ibid., 1914, 19, p. 459.
[20] Am. Jour. Physiol., 1915, 39, p. 131.
[21] Ibid., 1915, 36, p. 305.

The clotting time on addition of an optimum amount of calcium chlorid to the oxalated plasma was increased after shock, and varied as the coagulation time of the blood varied. When there was a decreased coagulation immediately following shock there was a corresponding decrease in the prothrombin time. Such variations might be caused by changes in prothrombin or by changes in thromboplastin. But since the same clotting time was obtained in both normal and in shock oxalated plasma when optimum amounts of thromboplastin and calcium were added there is probably no variation in prothrombin which would account for the changes in coagulability. This fact indicates changes in thromboplastin rather than in prothrombin. Barrat[22] believes that prothrombin has little influence on coagulation time, that with a sufficient concentration of prothrombin a given amount of thromboplastin will produce a definite quantity of thrombin independent of the actual concentration of prothrombin.

There has been an increasing interest in the rôle which lipoids play in immunologic reactions, and it is probable that lipoid changes play a very important part in anaphylactic shock. Howell[14] has shown that an important thromboplastic substance of the tissues is the lipoid cephalin and McLean[23] has shown that the thromboplastic activity of cephalin is directly proportional to its degree of unsaturation. Howell believes that the active substance of the tissues is probably a cephalin-protein combination. Dale and Walpole[24] have shown that when plasma or serum is treated with chloroform or trypsin a powerful thromboplastic activity is quickly produced. This is of interest in relation to the intravascular coagulation produced by serotoxin and kaolin and the increased coagulability sometimes found just after shock. These facts seem to indicate an immediate mobilization of thromboplastin. Tissue extracts when injected into animals produce the same characteristic symptoms seen in anaphylaxis. If there is a primary mobilization of thromboplastin it is rapidly neutralized or removed. Antithrombin will neutralize thromboplastin to a certain extent. If such a reaction takes place under these conditions, variations in the stability of the combination formed in different species of animals might determine whether or not there would be an increase in free antithrombin in the blood, or some animals may respond with a greater production of antithrombin.

[22] Biochem. Jour., 1915, 9, p. 511.
[23] Am. Jour. Physiol., 1917, 43, p. 586.
[24] Biochem. Jour., 1916, p. 10, p. 331.

These phenomena seem to be further indications for more extensive studies of the lipoids of the blood.

CONCLUSIONS

The changes in the coagulability of the blood during anaphylactic shock are due to changes in that stage of the coagulation process at which thrombin is formed through the interaction of prothrombin, calcium, thromboplastin and antithrombin (?). These changes are probably due to variations in thromboplastin.

Antithrombin changes are not great. In some animals there may be an increase in antithrombin which would aid in retarding the coagulation of the blood. There is no increase in antithrombin in rabbits.

There was a marked increase in the rate of fibrinolysis after anaphylactic and peptone shock.